## REMARKS

Claims 1-5 and 7-25 are pending.

### 35 USC § 101

Claims 1-5 and 7-25 are rejected under 35 U.S.C. §101. The Office Action asserts that no substantial or credible asserted utility or well established utility has been disclosed. The Examiner cites MPEP § 2701.02 IV [sic] and states that "where a stated utility is not specific or substantial, a prima facie showing must establish that it is more likely than not that a person of ordinary skill in the art would not consider that any utility asserted by the applicant would be specific and substantial. The prima facie showing must contain the following elements: (A) An explanation that clearly sets forth the reasoning used in concluding that the asserted utility for the claimed invention is neither both specific and substantial nor well-established; (B) Support for factual findings relied upon in reaching this conclusion; and (C) An evaluation of all relevant evidence of record, including utilities taught in the closest prior art".

Applicants respectfully request reconsideration of this rejection. Applicant's provided an explanation in the previous response, support was found in the specification itself as well as publications that used the methodology in the "real world". As is stated in MPEP § 2107.02 III.A., the "Langer" test is to be used in a utility determination. As stated in Langer:

> "As a matter of Patent Office practice, a specification which contains a disclosure of utility which corresponds in scope to the subject matter sought to be patented must be taken as sufficient to satisfy the utility requirement of § 101 for the entire claimed subject matter unless there is a reason for one skilled in the art to question the objective truth of the statement of utility or its scope."

As further stated in MPEP § 2107.02 III.A.,

> "[T]hus, Langer and subsequent cases **direct the Patent Office to presume that a statement of utility made by an applicant is true**. For obvious reasons of efficiency and in deference to an applicant's understanding of his or her invention, when a statement of utility is evaluated, Patent Office personnel should not begin an inquiry by questioning the truth of the statement of utility. Instead, **any inquiry must start by asking if there is any reason to question the truth of the statement of utility.** This can be done by evaluating the logic of the statements made, taking into consideration any evidence cited by the applicant. **If the asserted utility is credible (i.e., believable based on the record or the nature of the invention), a rejection based on "lack of utility" is <u>not</u> appropriate.** Thus, Patent Office personnel should not begin an evaluation of utility by assuming that an asserted utility is likely to be false, based on the technical field of the invention or for other general reasons.
>
> Compliance with § 101 is a question of fact. Thus, to overcome the presumption of truth that an assertion of utility by the applicant enjoys, Patent Office personnel must establish that it is more likely than not that one of ordinary skill in the art would doubt (i.e., "question") the truth of the statement of utility. To do this, Patent Office personnel must provide evidence sufficient to show that a person of ordinary skill in the art would consider the statement of asserted utility "false". A person of ordinary skill must have the benefit of both facts and reasoning in order to assess the truth of a statement. This means that if the applicant has presented facts that support the reasoning used in asserting a utility, Patent Office personnel must present countervailing facts

> and reasoning sufficient to establish that a person of ordinary skill would not believe the applicant's assertion of utility. The initial evidentiary standard used during evaluation of this question is a preponderance of the evidence (i.e., the totality of facts and reasoning suggest that it is more likely than not that the statement of the applicant is false)." (emphasis added).

As further outlined in MPEP § 2107.02. B:

> Where an applicant has specifically asserted that an invention has a particular utility, that assertion cannot simply be dismissed by Office personnel as being "wrong," even when there may be reason to believe that the assertion is not entirely accurate. Rather, Office personnel must determine if the assertion of utility is credible (i.e., **whether the assertion of utility is believable to a person of ordinary skill in the art based on the totality of evidence and reasoning provided). An assertion is credible unless (a) the logic underlying the assertion is seriously flawed, or (b) the facts upon which the assertion is based are inconsistent with the logic underlying the assertion.** Credibility as used in this context refers to the reliability of the statement based on the logic and facts that are offered by the applicant to support the assertion of utility.

It is respectfully submitted that the Examiner has not met this burden. The Examiner states that, "[a]s stated in the previous office action "...creating a library for further screening or testing is not a substantial and a specific utility....[t]he complex nature of said secondary structure, even for a known single compound, is known at times to defy such determination. The law clearly states that a patent is granted for a new and useful product...not prophetic or expedient statements; Nor one requiring further exploratory studies".

A mere statement that Applicant has not met the burden does not shift the burden of utility to Applicant. The Examiner has not provided countervailing facts and reasoning. Moreover, Applicant has provided an explanation and evidence of utility by use of third party publications that assert the utility of the method of Applicant specifically (DeGrado) and the state of the art of computational design techniques generally (Saven). Thus, Applicant has provided facts (2 publications by eminent persons in the field of computation design) that are sufficient to establish that a person skilled in the art would believe the assertion of utility.

MPEP § 2017.02 IV states, "the PTO must do more than merely question operability – it must set forth factual reasons which would lead on skilled in the art to question the objective truth of the statement of operability". Applicant respectfully submits that the Examiner has not provided factual reasons and further that Applicant has affirmatively provided evidence of the "objective truth of the statement of operability".

The Examiner states that "the complex nature and reliability of computational modeling results is at the heart of the [utility] issue since *in* silico modeling is not the equivalent of producing, testing and verifying the properties of a modified protein in a "real world" environment". The Examiner's basic position appears to be that methods of generating libraries *in silico*, without showing utility of the resulting library members, is without utility.

As a first point, this position would render all "research tools" unpatentable. For example, under this analogy, the PCR method would be unpatentable, as it would only be as useful if the nucleic acid sequences were "useful in the real world". Clearly, this is not the case, despite the fact that not all sequences obtained from PCR are "useful". Computational research tools are in fact patentable.

Secondly, while not important to the utility of the methods, the Applicants have shown that members of the generated libraries do in fact have utility.

As shown below, the Applicants have previously submitted two Exhibits that show that those of skill in the art find the computational methods developed by Xencor useful. In addition, the Applicants are submitting a number of press releases showing that computational methods developed by Xencor have resulted in major commercial deals between Xencor and Eli Lilly, Roche, Protein Design Labs, Genentech and Chugai, all highly sophisticated companies.

Applicant's again direct the Examiner's attention to In the article "Proteins from Scratch" (DeGrado, *Science* (1997), 278:80-81(Exhibit D from the previous response). Dr. DeGrado states (in describing an earlier version of Applicant's methodology):

> "Dahiyat...describe[s] a new approach that makes de novo protein design as easy as running a computer...Thus, the problem of de novo protein design reduced to two steps: selecting a desired tertiary structure and finding a sequence that would stabilize this fold. Dahiyat and Mayo have now mastered the second step with spectacular success. They have distilled the rules, insights and paradigms gleaned from two decades of experiments into a single computational algorithm...Thus the rules of ...computational methods for de novo design may now be sufficiently defined **to allow the engineering of a variety of proteins**." (emphasis added)

The Saven publication (Exhibit E from the prior response) shows that it is known in the art that combinatorial library generation has "real world use":

> "Not only can combinatorial methods be used for discovery but also, more deeply, they can inform our understanding of protein properties by generating and assaying whole ensembles of sequences. Traditionally, advances in structural biology have come from examining the structures of naturally occurring proteins, but with combinatorial experiments, **an enormous diversity of sequences can be generated at the control of the researcher**".

Also enclosed herein are press releases from the Xencor website (www.xencor.com) that show that a number of highly sophisticated and successful companies are collaborating with Xencor to utilize *in* silico computational methods for their needs. For example, Exhibit A is a press release about a research and license agreement between Torrey Mesa Research Institute (a wholly owned subsidiary of Syngenta), regarding the use of Xencor's computational technologies in protein design for food, pharmaceuticals and personal care. Exhibit B is a press release regarding a collaboration with Eli Lilly for the use of the computation technologies for designing therapeutic proteins. Exhibits C, D, E and F outline collaborations

with Genentech (Exhibit C), Roche (Exhibit D), Chugai (Exhibit E) and Protein Design Labs (Exhibit F) are for the use of Xencor's Xmab™ technology (a form of computational analysis directed to designing changes in antibodies computationally). Clearly, all of these companies are collaborating with Xencor because they think the computational analyses are "useful"; (note for example that Genentech is paying Xencor an upfront fee of $5M dollars).

In addition to these publications and press releasese that demonstrate the state of the art and the opinions of those of skill in the art regarding the usefulness of computational methods, the Examples in the specification also establish the utility. Applicant provided further "real world" use of computation design by citing **issued** patents that show the utility of this methodology. MPEP §2107.01 defines a ""substantial utility" as a "real world" use. Applicant has successfully used the claimed methods in the "real world" as shown in the publications cited as Exhibit E in the prior response.

As for "credibility", the Examiner has not shown (a) the logic underlying the assertion is seriously flawed, or (b) the facts upon which the assertion is based are inconsistent with the logic underlying the assertion, as is required by the MPEP (see above), while Applicant has provided credible explanation and documentation.

Applicant recites rational methods to design proteins that utilize well known structural information and physico-chemical properties to provide novel proteins having designed characteristics. These methods are in contrast to prior art techniques such as alanine scanning and gene "shuffling" which are not rational and require extensive experimentation to determine proteins' properties and sequence. The methodology has incorporated this information to address the "complex nature" of secondary structure. The method yields "real world" results, not "prophetic or expedient statements". This is shown in the examples in the specification, the "real world" examples as described in scientific publications, the recognition by highly sophisticated companies of this utility, and in the opinion of those skilled in the art.

Thus, the prima facie burden is shifted to the Examiner. The Examiner analogizes a library to a composition of matter, which has to undergo screening to isolate and identify a product, citing Brenner v. Manson, 148 USPQ 689 (1966) ("Brenner").

Applicants are specifically claiming a **method** of generating a secondary library, not a "library" per se, nor a composition of matter in the instant application. Assuming *arguendo* that Brenner is applicable, the secondary libraries are adequately defined and the method for generating them is fully enabled by the specification. The basis for this is that Applicant's are claiming a method of generating a secondary library. The library generated will necessarily vary with the particular target protein identified, as well as the use of the different parameters of the method. Moreover, certain other methods of generating a secondary library may be found in US 6,403,312, also assigned to Applicant and this patent was found to be enabling.

The arguments made above with respect to 35 USC §101 are equally applicable to the rejection under 35 USC §112, first paragraph. Thus, the discussions above regarding examples of actual utility by Applicant, as well as recognition to those skilled in the art of protein design and combinatorial library generation, meets the utility requirement under 35 USC § 101. It is submitted that the present invention has utility under §101 Applicants respectfully request that the rejection be withdrawn.

The Applicants submit that in light of the above argument, the claims are now in condition for allowance and an early notification of such is respectfully solicited. The Examiner is invited to contact the undersigned at (415) 781-1989 if any issues may be resolved in that manner.

Respectfully submitted,
DORSEY & WHITNEY LLP

Dated: April 4, 2005

By: Robin M. Silva

Four Embarcadero Center
Suite 3400
San Francisco, California 94111-4187
Telephone: (415) 781-1989
Fax No. (415) 398-3249

Robin M. Silva, Reg. No. 38,304

Customer No. 32940